Practitioner's Docket No. 4466-03

CHAPTER II

TRANSMITTAL LETTER TO THE UNITED STATES ELECTED OFFICE (EO/US)

(ENTRY INTO U.S. NATIONAL PHASE UNDER CHAPTER II)

PCT/GB97/02267	29 Sept. 1997	27 Sept. 1996
INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED

DIAGNOSIS OF SPONGIFORM DISEASE
TITLE OF INVENTION

Alan Ebringer
APPLICANT(S)

Box PCT
Assistant Commissioner for Patents
Washington D.C. 20231

ATTENTION: EO/US

NOTE: To avoid abandonment of the application, the applicant shall furnish to the USPTO, not later than 20 months from the priority date: (1) a copy of the international application, unless it has been previously communicated by the International Bureau or unless it was originally filed in the USPTO; and (2) the basic national fee (see 37 C.F.R. § 1.492(a)). The 30-month time limit may not be extended. 37 C.F.R. § 1.495.

CERTIFICATION UNDER 37 C.F.R. § 1.10*
(Express Mail label number is mandatory.)
(Express Mail certification is optional.)

I hereby certify that this Transmittal Letter and the papers indicated as being transmitted therewith is being deposited with the United States Postal Service on this date March 26, 1999, in an envelope as "Express Mail Post Office to Addressee" Mailing Label Number TB462926651US, addressed to the: Assistant Commissioner for Patents, Washington, D.C. 20231.

Judy Keeley
(type or print name of person mailing paper)

Judy Keeley
Signature of person mailing paper

WARNING: *Certificate of mailing (first class) or facsimile transmission procedures of 37 C.F.R. § 1.8 cannot be used to obtain a date of mailing or transmission for this correspondence.*

***WARNING:** Each paper or fee filed by "Express Mail" **must** have the number of the "Express Mail" mailing label placed thereon prior to mailing. 37 C.F.R. § 1.10(b).*
*"Since the filing of correspondence under § 1.10 without the Express Mail mailing label thereon is an oversight that can be avoided by the exercise of reasonable care, requests for waiver of this requirement will **not** be granted on petition." Notice of Oct. 24, 1996, 60 Fed. Reg. 56,439, at 56,442.*

WARNING: *Where the items are those which can be submitted to complete the entry of the international application into the national phase are subsequent to 30 months from the priority date the application is still considered to be in the international state and if mailing procedures are utilized to obtain a date the express mail procedure of 37 C.F.R. § 1.10 must be used (since international application papers are not covered by an ordinary certificate of mailing - See 37 C.F.R. § 1.8.*

NOTE: Documents and fees must be clearly identified as a submission to enter the national state under 35 U.S.C. § 371 otherwise the submission will be considered as being made under 35 U.S.C. § 111. 37 C.F.R. § 1.494(f).

99 MAR 02 AM 7:30

I. Applicant herewith submits to the United States Elected Office (EO/US) the following items under 35 U.S.C. § 371:

a. ☒ This express request to immediately begin national examination procedures (35 U.S.C. § 371(f)).

b. ☒ The U.S. National Fee (35 U.S.C. § 371(c)(1)) and other fees (37 C.F.R. § 1.492) as indicated below:

2. Fees

CLAIMS FEE	(1) FOR	(2) NUMBER FILED	(3) NUMBER EXTRA	(4) RATE	(5) CALCULATIONS
☐*	TOTAL CLAIMS 12	−20=		× $18.00=	$ −0−
	INDEPENDENT CLAIMS 3	−3=		× $78.00=	−0−
	MULTIPLE DEPENDENT CLAIM(S) (if applicable)			+ $260.00	
BASIC FEE**	☐ U.S. PTO WAS INTERNATIONAL PRELIMINARY EXAMINATION AUTHORITY Where an international preliminary examination fee as set forth in § 1.482 has been paid on the international application to the U.S. PTO: ☐ and the international preliminary examination report states that the criteria of novelty, inventive step (non-obviousness) and industrial activity, as defined in PCT Article 33(1) to (4) have been satisfied for all the claims presented in the application entering the national stage (37 C.F.R. § 1.492(a)(4)) ..... $96.00 ☐ and the above requirements are not met (37 C.F.R. § 1.492(a)(1)) ..... $670.00 ☒ U.S. PTO WAS NOT INTERNATIONAL PRELIMINARY EXAMINATION AUTHORITY Where no international preliminary examination fee as set forth in § 1.482 has been paid to the U.S. PTO, and payment of an international search fee as set forth in § 1.445(a)(2) to the U.S. PTO: ☐ has been paid (37 C.F.R. § 1.492(a)(2)) ..... $760.00 ☐ has not been paid (37 C.F.R. § 1.492(a)(3)) ..... $970.00 ☒ where a search report on the international application has been prepared by the European Patent Office or the Japanese Patent Office (37 C.F.R. § 1.492(a)(5)) $840.00				
	Total of above Calculations				= $840.00
SMALL ENTITY	Reduction by 1/2 for filing by small entity, if applicable. Affidavit must be filed also. (note 37 C.F.R. § 1.9, 1.27, 1.28)				−
	Subtotal				
	Total National Fee				$ 840.00
	Fee for recording the enclosed assignment document $40.00 (37 C.F.R. § 1.21(h)). (See Item 13 below). See attached "ASSIGNMENT COVER SHEET".				
TOTAL	Total Fees enclosed				$ 840.00

*See attached Preliminary Amendment Reducing the Number of Claims.

i. ☒ A check in the amount of $840.00 to cover the above fees is enclosed.

ii. ☐ Please charge Account No. _____ in the amount of $ _____. A duplicate copy of this sheet is enclosed.

***WARNING:** *"To avoid abandonment of the application the applicant shall furnish to the United States Patent and Trademark Office not later than the expiration of 30 months from the priority date: * * * (2) the basic national fee (see § 1.492(a)). The 30-month time limit may not be extended." 37 C.F.R. § 1.495(b).*

***WARNING:** *If the translation of the international application and/or the oath or declaration have not been submitted by the applicant within thirty (30) months from the priority date, such requirements may be met within a time period set by the Office. 37 C.F.R. § 1.495(b)(2). The payment of the surcharge set forth in § 1.492(e) is required as a condition for accepting the oath or declaration later than thirty (30) months after the priority date. The payment of the processing fee set forth in § 1.492(f) is required for acceptance of an English translation later than thirty (30) months after the priority date. Failure to comply with these requirements will result in abandonment of the application. The provisions of § 1.136 apply to the period which is set. Notice of Jan. 3, 1993, 1147 O.G. 29 to 40.*

3. ☒ A copy of the International application as filed (35 U.S.C. § 371(c)(2)):

NOTE: Section 1.495 (b) was amended to require that the basic national fee and a copy of the international application must be filed with the Office by 30 months from the priority date to avoid abandonment. "The International Bureau normally provides the copy of the international application to the Office in accordance with PCT Article 20. At the same time, the International Bureau notifies applicant of the communication to the Office. In accordance with PCT Rule 47.1, that notice shall be accepted by all designated offices as conclusive evidence that the communication has duly taken place. Thus, if the applicant desires to enter the national stage, the applicant normally need only check to be sure the notice from the International Bureau has been received and then pay the basic national fee by 30 months from the priority date." Notice of Jan. 7, 1993, 1147 O.G. 29 to 40, at 35-36. See item 14c below.

a. ☒ is transmitted herewith.

b. ☐ is not required, as the application was filed with the United States Receiving Office.

c. ☐ has been transmitted

i. ☐ by the International Bureau.
Date of mailing of the application (from form PCT/1B/308): _____.

ii. ☐ by applicant on _____.
Date

4. ☒ A translation of the International application into the English language (35 U.S.C. § 371(c)(2)):

a. ☐ is transmitted herewith.

b. ☒ is not required as the application was filed in English.

c. ☐ was previously transmitted by applicant on _____.
Date

d. ☐ will follow.

5. ☒ Amendments to the claims of the International application under PCT Article 19 (35 U.S.C. § 371(c)(3)):

NOTE: *The Notice of January 7, 1993 points out that 37 C.F.R. § 1.495(a) was amended to clarify the existing and continuing practice that PCT Article 19 amendments must be submitted by 30 months from the priority date and this deadline may not be extended. The Notice further advises that: "The failure to do so will not result in loss of the subject matter of the PCT Article 19 amendments. Applicant may submit that subject matter in a preliminary amendment filed under section 1.121. In many cases, filing an amendment under section 1.121 is preferable since grammatical or idiomatic errors may be corrected." 1147 O.G. 29-40, at 36.*

a. ☐ are transmitted herewith.

b. ☐ have been transmitted

i. ☐ by the International Bureau.
Date of mailing of the amendment (from form PCT/1B/308): _____.

ii. ☐ by applicant on (date) _____.
Date

c. ☒ have not been transmitted as

i. ☒ applicant chose not to make amendments under PCT Article 19.
Date of mailing of Search Report (from form PCT/ISA/210.): *_____.

ii. ☐ the time limit for the submission of amendments has not yet expired. The amendments or a statement that amendments have not been made will be transmitted before the expiration of the time limit under PCT Rule 46.1.

6. ☒ A translation of the amendments to the claims under PCT Article 19 (38 U.S.C. § 371(c)(3)):

a. ☐ is transmitted herewith.

b. ☐ is not required as the amendments were made in the English language.

c. ☒ has not been transmitted for reasons indicated at point 5(c) above.

7. ☒ A copy of the international examination report (PCT/IPEA/409)

☒ is transmitted herewith.

☐ is not required as the application was filed with the United States Receiving Office.

8. ☒ Annex(es) to the international preliminary examination report

a. ☒ is/are transmitted herewith.

b. ☐ is/are not required as the application was filed with the United States Receiving Office.

9. ☒ A translation of the annexes to the international preliminary examination report

a. ☐ is transmitted herewith.

b. X☒ is not required as the annexes are in the English language.

*Claims 3, 6 & 8 in the PCT Publication are hereby amended to delete multiple dependencies, as shown in the attached PCT Publication.

10. ☒ An oath or declaration of the inventor (35 U.S.C. § 371(c)(4)) complying with 35 U.S.C. § 115

a. ☐ was previously submitted by applicant on _____. Date

b. ☐ is submitted herewith, and such oath or declaration

i. ☐ is attached to the application.

ii. ☐ identifies the application and any amendments under PCT Article 19 that were transmitted as stated in points 3(b) or 3(c) and 5(b); and states that they were reviewed by the inventor as required by 37 C.F.R. § 1.70.

iii. ☒ will follow.

II. Other document(s) or information included:

11. ☒ An International Search Report (PCT/ISA/210) or Declaration under PCT Article 17(2)(a):

a. ☒ is transmitted herewith.

b. ☐ has been transmitted by the International Bureau. Date of mailing (from form PCT/IB/308): _____.

c. ☐ is not required, as the application was searched by the United States International Searching Authority.

d. ☐ will be transmitted promptly upon request.

e. ☐ has been submitted by applicant on _____. Date

12. ☒ An Information Disclosure Statement under 37 C.F.R. §§ 1.97 and 1.98:

a. ☐ is transmitted herewith.

Also transmitted herewith is/are:

☐ Form PTO-1449 (PTO/SB/08A and 08B).

☐ Copies of citations listed.

b. ☒ will be transmitted within THREE MONTHS of the date of submission of requirements under 35 U.S.C. § 371(c).

c. ☐ was previously submitted by applicant on _____. Date

13. ☐ An assignment document is transmitted herewith for recording.

A separate ☐ "COVER SHEET FOR ASSIGNMENT (DOCUMENT) ACCOMPANYING NEW PATENT APPLICATION" or ☐ FORM PTO 1595 is also attached.

_____

_____

_____

14. ☒ Additional documents:

a. ☐ Copy of request (PCT/RO/101)

b. ☒ International Publication No. WO 98/13694

i. ☒ Specification, claims and drawing

ii. ☐ Front page only

c. ☐ Preliminary amendment (37 C.F.R. § 1.121)

d. ☒ Other

International Search Report

International Preliminary Examination Report

15. ☒ The above checked items are being transmitted

a. ☒ before 30 months from any claimed priority date.

b. ☐ after 30 months.

16. ☐ Certain requirements under 35 U.S.C. § 371 were previously submitted by the applicant on _____, namely:

AUTHORIZATION TO CHARGE ADDITIONAL FEES

WARNING: *Accurately count claims, especially multiple dependant claims, to avoid unexpected high charges if extra claims are authorized.*

NOTE: "A written request may be submitted in an application that is an authorization to treat any concurrent or future reply, requiring a petition for an extension of time under this paragraph for its timely submission, as incorporating a petition for extension of time for the appropriate length of time. An authorization to charge all required fees, fees under § 1.17, or all required extension of time fees will be treated as a constructive petition for an extension of time in any concurrent or future reply requiring a petition for an extension of time under this paragraph for its timely submission. Submission of the fee set forth in § 1.17(a) will also be treated as a constructive petition for an extension of time in any concurrent reply requiring a petition for an extension of time under this paragraph for its timely submission." 37 C.F.R. § 1.136(a)(3).

NOTE: "Amounts of twenty-five dollars or less will not be returned unless specifically requested within a reasonable time, nor will the payer be notified of such amounts; amounts over twenty-five dollars may be returned by check or, if requested, by credit to a deposit account." 37 C.F.R. § 1.26(a).

☒ The Commissioner is hereby authorized to charge the following additional fees that may be required by this paper and during the entire pendency of this application to Account No. 08-0520 .

☒ 37 C.F.R. § 1.492(a)(1), (2), (3), and (4) (filing fees)

WARNING: *Because failure to pay the national fee within 30 months without extension (37 C.F.R. § 1.495(b)(2)) results in abandonment of the application, it would be best to always check the above box.*

☐ 37 C.F.R. § 1.492(b), (c) and (d) (presentation of extra claims)

NOTE: Because additional fees for excess or multiple dependent claims not paid on filing or on later presentation must only be paid or these claims cancelled by amendment prior to the expiration of the time period set for response by the PTO in any notice of fee deficiency (37 C.F.R. § 1.492(d)), it might be best not to authorize the PTO to charge additional claim fees, except possible when dealing with amendments after final action.

☒ 37 C.F.R. § 1.17 (application processing fees)

☒ 37 C.F.R. § 1.17(a)(1)–(5) (extension fees pursuant to § 1.136(a).

☐ 37 C.F.R. § 1.18 (issue fee at or before mailing of Notice of Allowance, pursuant to 37 C.F.R. § 1.311(b))

NOTE: Where an authorization to charge the issue fee to a deposit account has been filed before the mailing of a Notice of Allowance, the issue fee will be automatically charged to the deposit account at the time of mailing the notice of allowance. 37 C.F.R. § 1.311(b).

NOTE: 37 C.F.R. § 1.28(b) requires "Notification of any change in loss of entitlement to small entity status must be filed in the application . . . prior to paying, or at the time of paying . . . issue fee." From the wording of 37 C.F.R. § 1.28(b): (a) notification of change of status must be made even if the fee is paid as "other than a small entity" and (b) no notification is required if the change is to another small entity.

☒ 37 C.F.R. § 1.492(e) and (f) (surcharge fees for filing the declaration and/or filing an English translation of an International Application later than 30 months after the priority date).

SIGNATURE OF PRACTITIONER

Reg. No.: 32,243 (1)

DAVID H. JAFFER

Tel. No.: (408) 280-2800

(type or print name of practitioner)

Rosenblum, Parish & Isaacs

Customer No.:

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160 West Santa Clara Street, Fifteenth Floor
San Jose, California 95113

SCANNED

WO 98/13694

DIAGNOSIS OF SPONGIFORM DISEASE

This invention relates to the detection of spongiform encephalopathy and other demyelinating conditions in mammals and is particularly, but not exclusively, concerned with the diagnosis of bovine spongiform encephalopathy (BSE).

BSE is a recent neurological disorder of cattle, which was first reported in the U.K. after 1982, following a change in the preparation of "bone and meal" feeds. BSE has attracted some public concern, lest it be transmitted to humans following meat consumption. It has been suggested that BSE is caused by "prions", a type of infectious protein.

The present invention is based on an alternative model of the genesis of various forms of spongiform encephalopathy and other demyelinating conditions in mammals. According to the proposed model, BSE and related diseases are conceived as autoimmune diseases arising as a result of molecular mimicry between certain infective agents and the myelin of the infected mammal. This new model of BSE, in particular, is based on the following experimental observations.

A characteristic histopathological feature of BSE is a "spongiform" appearance, which also occurs in chronic but not acute "experimental allergic encephalomyelitis" (EAE), at least in rabbits and guinea pigs. A short sequence of bovine myelin (FSWGAEGQK), which withstands denaturation following heating to 100°C for one hour, was reported over twenty-five years ago to produce hind quarters paralysis, tremors and death, following inoculation into guinea pigs, which to some extent resembles the features observed in cattle suffering from BSE. In accordance with the present invention, this sequence has been used as a computer probe to search for proteins showing molecular mimicry. This sequence, in denatured form, may be described as encephalitogenic.

Analysis of proteins in databases (Genbank and SwissProt) revealed that 3 microbes showed molecular mimicry of the bovine myelin sequence , the best one being found in 4-carboxy-muconolactone-decarboxylase of Acinetobacter calcoaceticus, a common microbe present in soil and water supplies. These sequence similarities are shown in the following Table.

Comparison of amino acids of bovine myelin to microorganisms from Genbank and SwissProt which have similar sequences in other proteins.

Source	Amino acids	Positions	Locations
Bovine myelin	LSRFSWGAE	110 - 118	
Acinetobacter calcoaceticus	ISRFAWGEV	41 - 49	4-carboxy-muconolactone decarboxylase
Agrobacter tumefaciens	YTRFTWGAP	693 - 701	Beta-glucosidase
Ruminococcus albus	YTQFEISAE	274 - 282	Beta-glucosidase

Alphabetic letters refer to biochemical symbols for amino acids.

In conformity with the new model, it has now been found that sera of BSE affected cattle contain significantly high levels of antibodies to Acinetobacter species.

The present invention therefore provides a diagnostic test for spongiform encephalopathy and other demyelinating conditions in mammals which comprises assaying antibodies present in the mammal which bind to an antigenic peptide which exhibits molecular mimicry of a mammalian myelin peptide, especially one having the sequence FSWGAEGQK. The term "molecular mimicry" refers to a degree of similarity (sequence homology) as between the antigenic peptide and a myelin peptide which results in the formation of antibodies which cross-react with myelin and demyelinate nervous tissue. The presence of such antibodies at elevated levels compared to

those found in unaffected animals is therefore a marker for BSE which may be used to detect BSE at an early stage at which curative or other appropriate action may be taken.

The assay may be carried out using the whole Acinetobacter or other organism as the test antigen. Any strain of Acinetobacter having the antigenic peptide identified above may be used. Alternatively the isolated peptide or a synthetic form of the peptide may be used as antigen. Any suitable type of assay procedure may be used, the ELISA method being especially convenient.

Antibody levels indicative of BSE are those which are significantly higher than the control levels. Usually, levels elevated to about 2 standard deviations above the controls may be taken as a positive indication but margins around this figure may be possible or desirable for purposes of caution.

Procedures for carrying out an assay in accordance with this invention are described in the following illustrative Example, based on comparison of sera from animals known to have had BSE with sera from healthy animals.

MATERIALS AND METHODS

Bovine sera

Sera from 29 animals, which were found at post-mortem to satisfy the criteria of BSE and 18 animals which did not, were supplied by the Central Veterinary Laboratory (CVL) (New Haw, Addlestone, Surrey), an executive agency of the U.K. Ministry of Agriculture, Fisheries and Food (MAFF). The 18 animals which did not have BSE had been referred to CVL because of abnormal behaviour but post-mortem examinations carried out by MAFF had excluded BSE.

Furthermore, 30 sera from animals aged less than 30 months (A<30M) (8 Friesians, 21 Hereford-Friesian and 1 Charolais-Friesian crossbreeds) and 28 sera from animals aged more than 30 months (A>30M) (all dairy Friesians), were used as further controls. These were collected

from a farm, kept under "organic farming" conditions where no case of BSE had been reported. Serum samples were obtained during routine herd testing.

Preparation of bacteria

Acinetobacter calcoaceticus was obtained from the National Collection of Industrial and Marine Bacteria Ltd. NCIMB 10694 (Aberdeen). Cultures were grown in 21 flasks on an orbital shaker for 2 days at 30°C, in 200 ml nutrient broth (Oxoid; 25 g/l). Flasks were inoculated with 10 ml of the corresponding starter culture left shaking at 37°C for 6 hours. Batch culture cells were harvested by centrifugation at 6000 r.p.m. for 20 minutes at 4°C (MSE 18.6 x 250 ml rotor). The pellets of cells were then washed three times with 0.15 M phosphate-buffered saline (PBS; pH 7.4) before being finally resuspended in 20 ml of PBS. A stock solution of the suspension was prepared by diluting in 0.05 M carbonate buffer (pH 9.6) to give an optical density (OD) reading of 0.25 on the spectrophotometer (Corning Model 258).

Enzyme-linked immunosorbent assay

ELISA assays were carried out in the conventional manner. Briefly ELISA plates were coated with bacteria overnight at 4°C and the non-specific sites blocked with PBS containing 0.1% Tween, 0.2% ovalbumin (Sigma, Grade III), plates washed and a 1/200 dilution of test or control serum added. The plates were incubated at 37°C for 1 hour, washed and rabbit anti-cow immunoglobulin (IgG + IgA + IgM) (1:4000) (Dako Ltd.) added. The plates were reincubated for 2 hours, washed and substrate added. The reaction was stopped with a 2 mg/ml solution of sodium fluoride (Sigma). The plates were read at 630 nm on a microtitre plate reader (Dynatech MR 600) and results expressed as OD ± S.E. All studies were carried out under code in that the tester did not know which were test or control sera. The mean OD units of total immunoglobulin antibodies in different groups were compared using Student's t-test.

ELISA METHOD SHEET

1. Dilute antigen in coating buffer, add 200μl to each well. Incubate overnight at 4°C wrapped in foil.
2. Wash out the antigen, using washing/incubation buffer; the wells of the tray should be completely full during the washing stages as the Tween-20 prevents any further protein from being absorbed onto the plastic. Wash 3 times, leaving for approx. 4 minute intervals at room temperature.
3. Incubate the plate at 37°C for 1hr with 0.2% Ovalbumin in washing/incubation buffer.
4. Add 200μl of test serum. Dilutions are made in washing/incubation buffer. Incubate for 2 hours at 37°C wrapped in foil.
5. Repeat washing process as in 2.
6. Add 200μl Horseradish peroxide HRP-conjugated second antibody, also diluted in washing/incubation buffer.
7. Repeat washing process as in 2.
8. Add 200μl substrate (ABTS) to wells; leave to develop colour for approx. 20 minutes in the dark at room temperature Stop reaction with 100μl of stopping solution and read plate at 630nm.

RESULTS

Antibodies to A. calcoaceticus of total immunoglobulin (IgG – IgA + IgM) were significantly elevated in the BSE sera (mean ± SE: 0.99 ± 0.05) when compared to CVL controls (0.65 ± 0.06) ($t = 4.48$, $p<0.001$), organic farming controls aged more than 30 months (0.57 ± 0.03) ($t = 7.19$, $p<0.001$) and organic farming controls aged less than 30 months (0.53 ± 0.02) ($t = 8.64$, $p<0.001$). These results are shown in the attached Figure.

Legend to figure:

Antibody titres (bar = mean) for 30 controls aged less than 30 months (A<30m), 28 controls aged more than 30 months (A>30m), 18 controls from the Central Veterinary Laboratory (CVL) compared to 29 BSE sera, when tested against Acinetobacter calcoaceticus (Figure la) and E.coli (Figure lb). (Dashed line represents 95% confidence limits for mean of controls: A<30m + A>30m - one tailed test) (OD = optical density).

There was no significant difference between the CVL controls and the organic farming controls aged more than 30 months, but there was a small, statistically significant difference with the sera from animals aged less than 30 months ($t = 2.41$, $p < 0.05$). A re-examination of the CSL control serum with the highest anti-Acinetobacter level of 1.16 OD, showed that it came from a clinically normal control animal diagnosed as negative to BSE on the statutory diagnostic criteria, and it was also negative when tested for scrapie associated fibrils. This case did however have white matter vacuolation of the substantia nigra and internal capsule, although this had been seen before and not considered significant.

One clear result from these studies, is that in at least in one "transmissible spongiform encephalopathy" (TSE), namely BSE, a specific immune response can be demonstrated against a microbe that is found readily in the environment of cattle and which also happens to possess a molecular sequence resembling bovine myelin.

Other forms of spongiform encephalopathy including Creuzfeld Jacob disease (CJD) and Multiple Sclerosis (MS) are open to explanation on the same model as indicated for BSE. CJD sera and MS sera are currently under test to confirm the presence of cross-reacting antibodies.

CLAIMS

1. A diagnostic test for spongiform encephalopathy and other demyelinating conditions in mammals which comprises assaying antibodies present in the mammal which bind to an antigenic peptide which exhibits molecular mimicry of a mammalian myelin peptide.

2. A test according to Claim 1, in which the mammalian myelin peptide has the sequence FSWGAEGQK.

3. A test according to Claim 1 ~~or 2~~ for BSE in cattle.

4. A test according to Claim 3, using as the test antigen whole bacteria of an Acinetobacter, Agrobacterium or Ruminococcus species.

5. A test according to Claim 4, using bacteria of the species Acinetobacter calcoaceticus, Agrobacterium tumefaciens, or Ruminococcus albus.

6. A test according to Claim 3, using as the test antigen a peptide derived from bacteria specified in Claim 4 ~~or 5~~.

7. A test according to Claim 6, using a peptide of sequence ISRFAWGEV, YTRFTWGAP, or YTQFEISAE.

8. A test according to Claim 6 ~~or 7~~, in which the peptide used is a synthetic peptide.

9. A method of testing for BSE in cattle which comprises assaying sera collected from the cattle for antibodies to a species of Acinetobacter, Agrobacterium or Ruminococcus, or a peptide having a sequence present in said species which mimics a peptide of bovine myelin and identifying animals having a level of antibodies at least about two standard deviations above that of healthy control animals.

10. A method according to claim 9, in which the bovine myelin peptide has the sequence FSWGAEGQK.

11. A diagnostic test kit for BSE in cattle comprising as test antigen a species of Acinetobacter, Agrobacterium or Ruminococcus, or a peptide having a sequence present in said species which mimics a peptide of bovine myelin.

12. A test kit according to claim 11, in which the test antigen is a peptide which mimics the sequence FSWGAEGQK.

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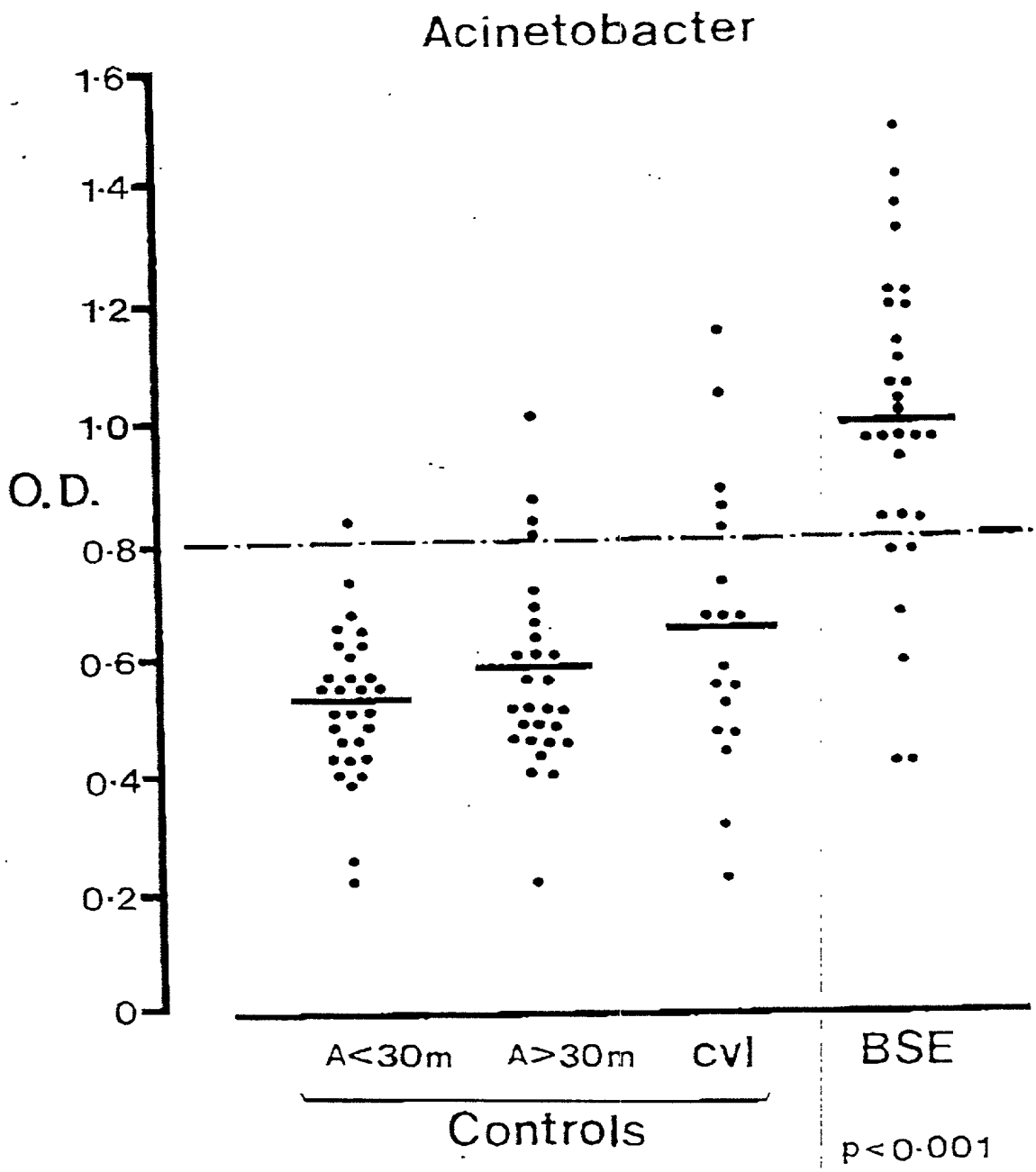
WO 98/13694

PCT/GB97/02667



COMBINED DECLARATION, POWER OF ATTORNEY & PETITION

DECLARATION

As a below-named inventor, I hereby declare that:

(i) my residence, post office address and citizenship are as stated below next to my name;

(ii) I have reviewed and understand the contents of the attached specification including the drawing and claims as amended by any amendment referred to below;

(iii) I believe I am the original, first and sole inventor (if only one is listed below) or a joint inventor (if plural inventors are named below) of the invention entitled:

DIAGNOSIS OF SPONGIFORM DISEASE

as described and claimed in the specification which

☐ is attached hereto.

☐ was filed on _____ as U.S. Patent Application Serial No. _____ amended on _____.

☒ was described and claimed in PCT International Application No. PCT/GB97/02267 filed on 29 September 1997 and entered into U.S. National Phase Under Chapter II on 26 March 1999, as U.S. Application No. 09/269,607

(iv) I acknowledge my duty to disclose information of which I am aware which is material to the examination of this application, in accordance with 37 CFR 1.56(a);

(v) I do not know and do not believe that the same was (1) ever known or used in the United States before my or our invention thereof, or (2) patented or described in any printed publication in any country before my or our invention thereof for more than one year prior to this application, or (3) in public use or on sale in the United States more than one year prior to this application;

I declare further that all statements made above of my own knowledge are true and all statements made on information and belief are believed to be true; and these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

POWER OF ATTORNEY

I hereby appoint the following patent attorneys and/or patent agent(s) with full power of appointment, substitution and revocation to prosecute this application, to make alterations and amendments thereto, to receive the patent, and to transact all business in the Patent Office connected therewith.

DAVID H. JAFFER, Reg. No. 32,243

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PETITION

Wherefore, I pray that Letters Patent be granted to me for the invention or discovery described and claimed in the above-mentioned specification and claims, and I hereby subscribe my name to the foregoing Declaration, Power of Attorney & Petition with references to the above-mentioned specification and claims.

SIGNATURES

1-DD

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Date: 22ND JULY 1999